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SUSCEPTIBILITY

Manogepix (APX001A) *In Vitro* Activity against *Candida auris*: Head-to-Head Comparison of EUCAST and CLSI MICs

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ABSTRACT Fosmanogepix is a novel prodrug in a new class of antifungal agents. Manogepix is the active moiety. We evaluated the CLSI and EUCAST MICs of manogepix and eight comparators against *Candida auris*. CLSI M27-A3 susceptibility testing of manogepix was performed for 122 *C. auris* isolates and compared to CLSI and EUCAST MICs for manogepix and eight comparators. Differences and agreement were calculated for each compound. Wild-type upper limits (WT-ULs; the upper MIC where the wild-type distribution ends) for manogepix and correlations with other drugs' MICs were determined. Manogepix MICs (CLSI/EUCAST [mg/liter]) and WT-ULs were as follows: MIC_{50}s, 0.008/0.016; MIC_{90}s, 0.03/0.03; ranges, 0.001 to 0.25/0.001 to 0.125; 97.5% and 99% WT-ULs, 0.03/0.125 and 0.06/0.125, respectively. The manogepix CLSI/EUCAST MIC distributions spanned 9/8 dilutions, respectively. Significant correlation was found for all azoles, particularly fluconazole ($r = 0.22$ to 0.74, $P < 0.05$). Isolates with EUCAST manogepix MICs of ≤0.004 had 7.6-/10.2-fold-lower fluconazole CLSI/EUCAST MICs than the remaining isolates that had higher manogepix MICs. The highest essential agreement between CLSI and EUCAST results was observed for manogepix and fluconazole, with a median difference of −1 to 0 2-fold dilutions, 90th percentile absolute difference of 1, and 90 to 92% and 98 to 100% agreement within ±1 and ±2 dilutions. The lowest agreements within ±1 and ±2 dilutions were found for isavuconazole and anidulafungin (44 to 50% and 69 to 76%). The correlation between CLSI and EUCAST manogepix MICs against *C. auris* was excellent. Differential MICs were found, and these correlated with fluconazole MICs, suggesting that the *C. auris* population is a mix of wild-type isolates and non-wild-type isolates with low-grade manogepix MIC elevation, probably involving efflux pump expression. However, manogepix was the most potent agent against *C. auris* in this *in vitro* study.

KEYWORDS APX001A, manogepix, fosmanogepix, APX001, candidemia, antifungal susceptibility, EUCAST, CLSI, fluconazole, amphotericin B, echinocandins

Manogepix (APX001A) is the active moiety of the novel drug candidate fosmanogepix (APX001), currently in clinical trials for the treatment of invasive fungal infections. Manogepix has demonstrated activity against a wide range of human-pathogenic fungi, including multidrug-resistant *Candida auris* (1–4). Fosmanogepix has been granted fast track designations by the U.S. Food and Drug Administration (FDA) for seven indications, including invasive candidiasis. It is currently in phase 2 clinical trials (ClinicalTrials.gov identifier) for *C. auris* infections (NCT04148287), invasive aspergillosis (NCT04148287), and invasive candidiasis/candidemia (NCT03604705).

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TABLE 1 Comparative CLSI and EUCAST MICs of nine antifungal drugs against *C. auris*

Drug[a]	MIC_{50}/geometric mean (range), MIC_{90} (mg/liter)		Dilution differences [median (range), 90th percentile of absolute differences][b]	% agreement within indicated no. of dilutions		
	CLSI	EUCAST		Zero	±1	±2
MGX	0.008/0.01 (0.001 to 0.25), 0.03	0.016/0.014 (0.001 to 0.125), 0.03	−1 (−2 to 2), 1	29	90	100
AMB	0.5/0.674 (0.125 to 8), 1	1/0.918 (0.5 to 1), 1	−1 (−3 to 3), 2	40	81	97
ANI	0.125/0.222 (0.016 to 8), 0.5	0.125/0.196 (0.001 to 64), 1	0 (−9 to 7), 3	18	50	69
MFG	0.125/0.12 (0.016 to 8), 0.25	0.125/0.155 (0.016 to 64), 0.25	0 (−10 to 6), 2	36	76	90
FLU	256/220.6 (4 to 512), 512	256/221.6 (1 to >256), 512	0 (−3 to 2), 1	63	92	98
VOR	1/0.698 (0.03 to 16), 4	0.5/0.554 (0.004 to 4), 2	0 (−5 to 7), 3	26	64	83
POSA	0.016/0.035 (0.016 to 8), 0.125	0.03/0.036 (0.004 to 0.5), 0.125	0 (−5 to 9), 3	19	63	83
ISA	0.125/0.102 (0.016 to 4), 0.5	0.125/0.091 (0.004 to 2), 0.5	0 (−5 to 10), 4	15	44	76
ITRA	0.125/0.115 (0.03 to 2), 0.25	0.125/0.131 (0.004 to 1), 0.5	0 (−3 to 5), 2	24	66	92

[a]MGX, manogepix; AMB, amphotericin B; ANI, anidulafungin; MFG, micafungin; FLU, fluconazole; VOR, voriconazole; POSA, posaconazole; ISA, isavuconazole; ITRA, itraconazole.
[b]High off-scale MICs were converted to the next-higher 2-fold dilution. The 90th percentile was calculated from the absolute differences.

Fosmanogepix has been evaluated *in vivo* and proven efficacious against *C. auris* in immunosuppressed mouse models when therapy is initiated early, as well as when delayed for 24 h (4–6). The 24-h free-drug area under the concentration-time curve (AUC)/MIC ratio has been identified as the pharmacokinetics (PK)/pharmacodynamics (PD) index that best correlated with outcome and targets for stasis and is established as follows: 14.67 ± 8.30 (mean ± standard deviation [SD]) for *C. auris*, compared to 20.60 ± 6.50 for *Candida albicans* and 1.31 ± 0.27 for *Candida glabrata* (5).

The *in vitro* susceptibility of *C. auris* to manogepix has been previously investigated using the CLSI reference methodology in four studies, three of which included 16 or fewer isolates. Presented as the MIC_{50}, MIC_{90} (MIC range), Berkow and Lockhart reported 0.002 mg/liter, 0.008 mg/liter (<0.0005 to 0.015 mg/liter) in a study including 100 isolates from four clades (1); Hager et al. reported 0.004 mg/liter, 0.03 mg/liter (0.002 to 0.06 mg/liter) in a study including 16 isolates (4); Wiederhold et al. reported 0.03 mg/liter, 0.03 mg/liter (≤0.002 to 0.03 mg/liter) in a study including 13 isolates (6), and finally, Pfaller et al. included a single isolate with a MIC of 0.06 mg/liter (3). In contrast, only a single study investigated the susceptibility by the EUCAST E.Def 7.3.1 method, reporting the following MIC_{50}, MIC_{90} (MIC range): 0.008 mg/liter, 0.03 mg/liter (0.001 to 0.125 mg/liter) (2). MIC_{50} and modal MIC values in general reflect the typical MIC for a given species as long as the majority of isolates are wild type (WT) to the compound in question. Consequently, differences in these values normally reflect differences in susceptibility testing method or interlaboratory variation associated with technical issues. For *C. auris* specifically, clonal outbreaks have occurred and been associated with four different major *C. auris* clusters of South American, South Asian, African, and East Asian origins (7). A potential fifth clade of Iranian origin has been described recently (8). Isolates from four clusters have been associated with differential susceptibilities to amphotericin B and, most notably, to fluconazole, and different mutations in the *erg11* azole target gene have been associated with different clades (7, 8). Here, we investigated the method-specific agreement between MICs obtained using CLSI and EUCAST reference methods when testing manogepix and eight comparators against a collection of 122 *C. auris* isolates.

RESULTS

Manogepix MICs. Manogepix MICs against *C. auris* were low and, in general, 1 2-fold dilution lower using the CLSI versus the EUCAST method, with the following key parameters, indicated as CLSI/EUCAST (mg/liter): MIC_{50}s, 0.008/0.016; MIC_{90}s, 0.03/0.03; ranges, 0.001 to 0.25/0.001 to 0.125; statistical wild-type upper limits (WT-ULs) encompassing 97.5% and 99% of the fitted population, 0.03/0.125 and 0.06/0.125, respectively (Tables 1 and 2). At the individual isolate level, the agreements between CLSI and EUCAST MICs were excellent, with MICs within ±1 dilutions in 90% of the cases and

within ±2 dilutions for 100%. The manogepix MIC distributions spanned 9 and 8 dilutions for the CLSI and EUCAST methods, respectively. Both MIC distributions were slightly asymmetrical due to a tail to the left of the modal MIC (Fig. 1). Moreover, both MIC distributions, but particularly the one for CLSI, were truncated at the lowest concentration tested (0.001 mg/liter), suggesting that the true MIC distributions might have been wider if lower concentrations had been tested. Twenty isolates had low EUCAST manogepix MICs of ≤0.004 mg/liter (Table 2). By CLSI/EUCAST, these isolates were also 7.6-/10.2-fold more susceptible to fluconazole than the remaining isolates, with geometric mean (range) fluconazole MICs of 40.8 (4 to 512)/32.0 (1 to 512) mg/liter versus 310.8 (64 to 512)/326.3 (64 to 512) mg/liter, respectively (Fig. 2). Significant correlations between manogepix MIC and the MICs of the other drugs were found using the CLSI method with fluconazole ($r = 0.53$, $P < 0.001$), voriconazole ($r = 0.22$, $P = 0.017$), isavuconazole ($r = 0.22$, $P = 0.017$), and itraconazole ($r = 0.22$, $P = 0.016$) and for EUCAST with fluconazole ($r = 0.74$, $P < 0.001$), voriconazole ($r = 0.58$, $P < 0.001$), isavuconazole ($r = 0.64$, $P < 0.001$), itraconazole ($r = 0.66$, $P < 0.001$), and posaconazole ($r = 0.44$, $P < 0.001$) (Fig. 3).

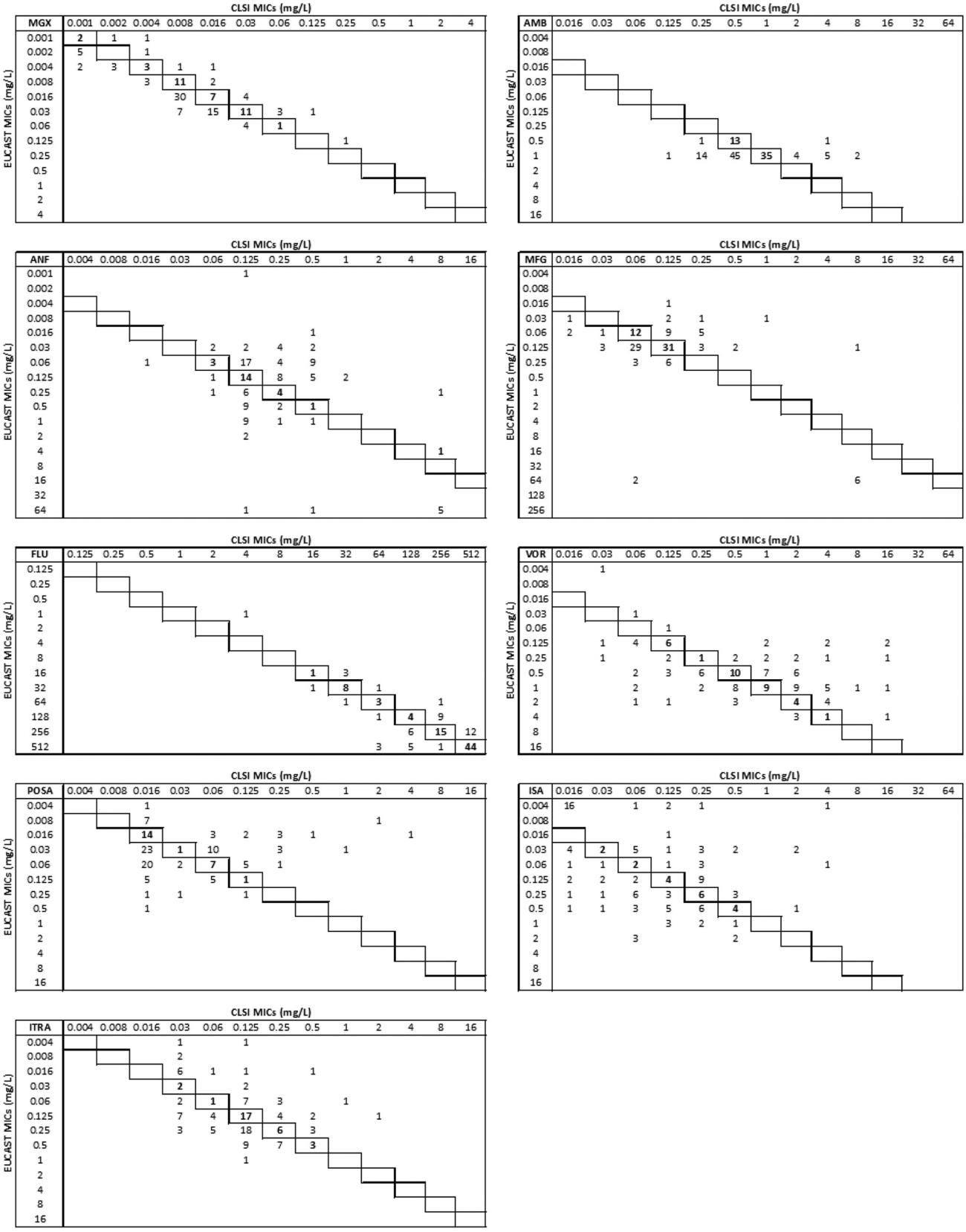
Agreement between CLSI and EUCAST MICs for manogepix and comparators. Comparing CLSI and EUCAST MICs pairwise for each compound, statistically significant correlations were found for all drugs ($r > 0.40$, $P < 0.001$) except posaconazole ($r = -0.03$, $P = 0.67$) and amphotericin B ($r = 0.10$, $P = 0.27$). No significant differences were found between CLSI and EUCAST MICs for each compound. The highest agreement across CLSI and EUCAST methods was observed for manogepix and fluconazole, with a median difference of −1 to 0 2-fold dilutions, a 90th percentile absolute difference of 1, and in both cases, ≥90% agreement within ±1 dilution (Table 1). The agreement was also high for amphotericin B and micafungin, ranging from 76 to 81% and 90 to 97% within ±1 and ±2 dilutions, respectively. The agreement was less optimal for itraconazole, voriconazole, and posaconazole (ranging from 63 to 66% and 83 to 92% within ±1 and ±2 dilutions, respectively), and low for isavuconazole and anidulafungin (ranging from 44 to 50% and 69 to 76% within ±1 and ±2 dilutions, respectively, Table 1).

DISCUSSION

We found an excellent essential agreement between manogepix MICs determined by the CLSI and EUCAST reference methodologies when a collection of 122 *C. auris* isolates was tested in two different laboratories. Compared to the results for the eight other antifungal compounds included in our study, the essential agreement was highest for manogepix and fluconazole and lowest for anidulafungin and isavuconazole.

The CLSI and EUCAST MIC distributions for manogepix against *C. auris* were quite broad, spanning 9 and 8 dilutions, respectively, and potentially more due to an apparent truncation at the low end. Wide distributions normally reflect either suboptimal intralaboratory reproducibility of the MIC testing, which appears contradictory to the excellent agreement found between the MICs, or differential susceptibilities among the isolates tested. Manogepix targets an essential fungal acyltransferase, Gwt1 (9), blocking inositol acylation of glycosylphosphatidylinositol (GPI) anchors and trafficking of GPI-anchored proteins from the endoplasmic reticulum (ER) (10). It is not yet in clinical use, and therefore, differential susceptibility was unexpected, as these clinical isolates have no prior exposure to manogepix. However, recent studies have demonstrated a correlation between fluconazole and manogepix MICs for other *Candida* species (2). Moreover, two mutants selected *in vitro* for elevated manogepix MICs also demonstrated a 4-fold and a 2-fold increase in fluconazole MICs, which was mediated by increased expression of multidrug efflux pumps. Specifically, one *Candida parapsilosis* and one *C. albicans* mutant showed activated expression of the major facilitator superfamily transporter gene *MDR1* and of the ATP-binding cassette transporter genes *CDR11* and *SNQ2*, respectively (11, 12). This is in line with the significant correlation between manogepix MICs and all azole MICs, particularly with EUCAST methodology. The majority of the Indian *C. auris* isolates included here were fluconazole resistant, and

TABLE 2 Comparative MIC distributions of nine antifungal drugs obtained with CLSI and EUCAST methods against *C. auris*[a]



[a]Framed cells represent the identity lines where the MICs are the same between the two methods. MGX, manogepix; AMB, amphotericin B; ANI, anidulafungin; MFG, micafungin; FLU, fluconazole; VOR, voriconazole; POSA, posaconazole; ISA, isavuconazole; ITRA, itraconazole.

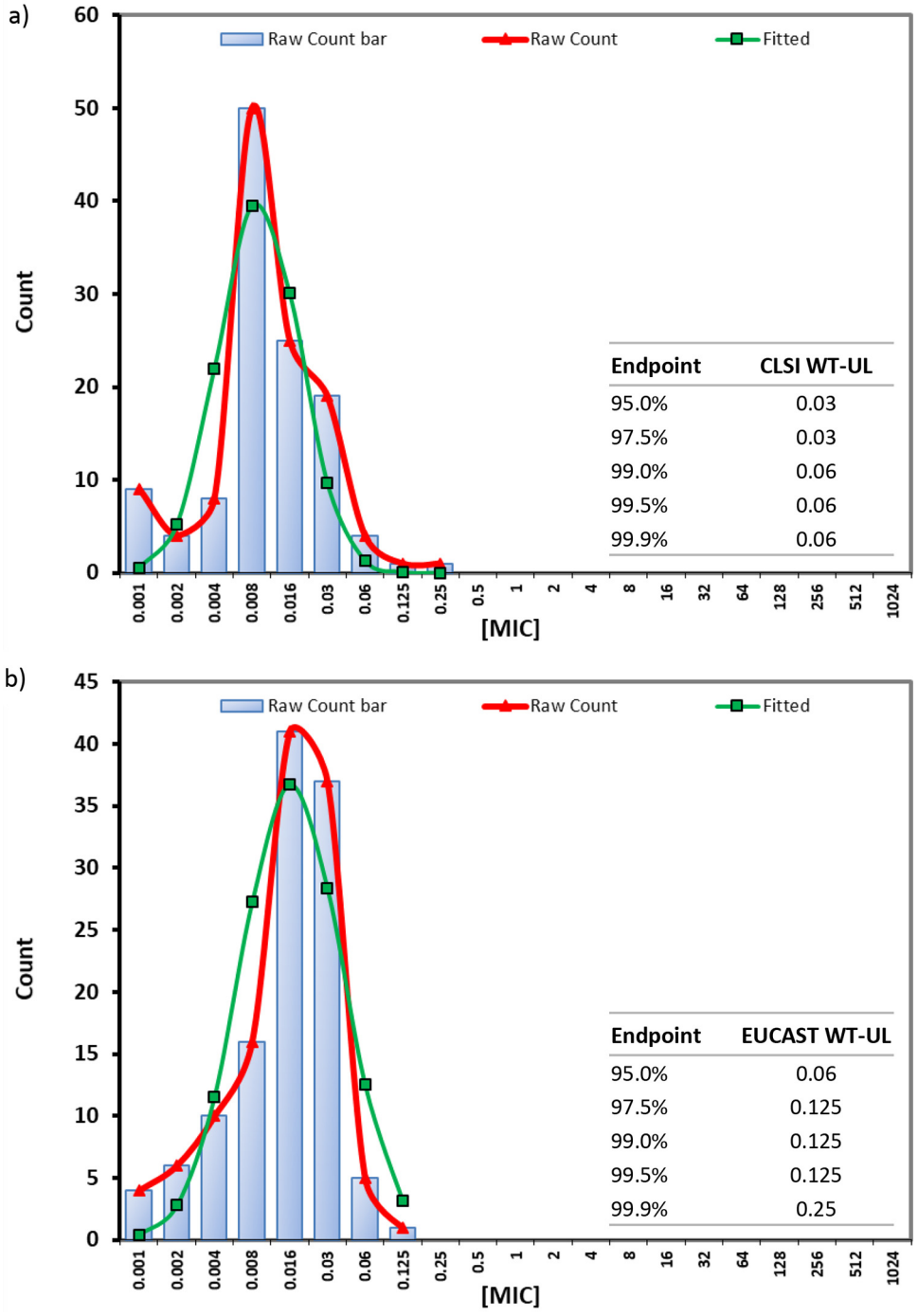


FIG 1 Manogepix MICs (mg/liter) against 122 *C. auris* isolates determined by the CLSI (a) and EUCAST (b) reference methods. The ECOFFs (mg/liter) determined using ECOFFinder XL 2.0, including various proportions of the fitted population, are indicated for both methods in the embedded tables.

when the fluconazole MICs were compared for isolates with low and high manogepix MICs, a significant correlation was observed between manogepix and fluconazole MICs. Fluconazole resistance in *C. auris* was first related to Y132F (a change of Y to F at position 132), K143R, and F126T alterations in the Erg11 target protein (7, 13), but involvement of efflux pumps and target gene upregulation have subsequently been demonstrated in aging cells (14). Taken together, we therefore hypothesize that the differential susceptibilities to fluconazole may explain the wide manogepix MIC distri-

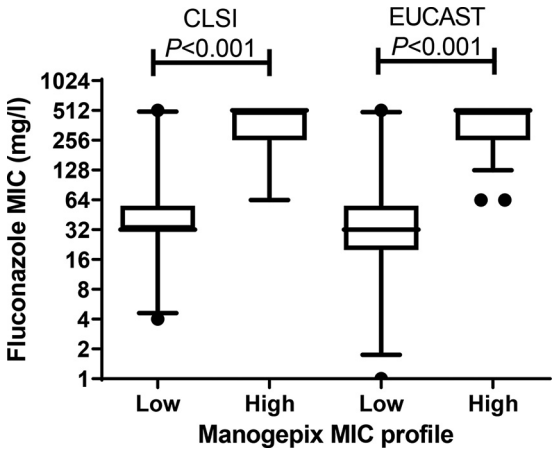


FIG 2 Comparison of fluconazole CLSI and EUCAST MICs for isolates with low (≤0.004 mg/liter) and high (0.008 to 0.125 mg/liter) EUCAST MIC profiles. Whiskers show 5th to 95th percentiles.

bution observed for *C. auris* and that both CLSI and EUCAST testing of manogepix against *C. auris* are robust and reproducible. This also implies that our isolates include both a minor true wild-type population (with very low MICs) and a larger non-wild-type population (with slightly elevated manogepix MICs) and thus, that in principle, future epidemiological cutoff (ECOFF) setting for this species may be difficult. Importantly, however, the manogepix MIC variation among these populations is low compared to the variation among wild-type and non-wild-type isolates for the azoles, which span up to at least 11 dilutions. Therefore, the highest manogepix MICs among the isolates are much less elevated than the fluconazole MICs for the most azole-resistant isolates (0.25 mg/liter compared to 4 to 512 mg/liter). The clinical implications for the elevation of manogepix MIC values are unknown and will be informed by the patient outcomes in the clinical development program.

We observed a discrete but systematic difference between CLSI and EUCAST endpoints, with CLSI MICs being 1 2-fold dilution lower than EUCAST MICs. In comparison to published data, Berkow and Lockhart reported 2 2-fold-dilution-lower CLSI MICs than were found with CLSI in this study (MIC_{50}s of 0.002 versus 0.008 mg/liter) for 100 isolates from four clades (1). Those isolates were selected to represent different *C. auris* clades and patterns of susceptibility to other antifungal agents, and the manogepix MIC distribution was multimodal, with a fifth of the isolates at <0.0005 mg/liter, a peak at 0.001 mg/liter, and another peak spanning 0.004 to 0.008 mg/liter (20 isolates at 0.004 and 19 at 0.008 mg/liter). This may suggest that the overall lower MICs reported in the Berkow and Lockhart study may be explained by more isolates belonging to clades with lower MICs rather than by interlaboratory variation. However, a multicenter study testing a shared strain collection is warranted to clarify whether interlaboratory variability also plays a role.

Our study has limitations. First, we have not characterized the mechanism behind the azole resistance in our isolates. Thus, it is unclear whether efflux pumps, which have been associated with MIC elevation for both manogepix and fluconazole in other *Candida* species, were highly expressed in our isolates. Second, the MIC determinations were performed in two separate laboratories, and thus, the 1 2-fold-dilution difference observed between the CLSI and EUCAST data set may be related to factors other than method differences, such as differential potencies of the stock solution, binding to plasticware, etc. On the other hand, it is also a strength that an excellent essential agreement was found despite tests being performed in separate laboratories. Third, our lowest concentration tested for manogepix was 0.001 mg/liter, and 10 and 4 isolates had MICs at or lower than this value with CLSI and EUCAST, respectively. However, as this is a small fraction of the isolates, it is not likely that this alters the conclusion drawn in this study.

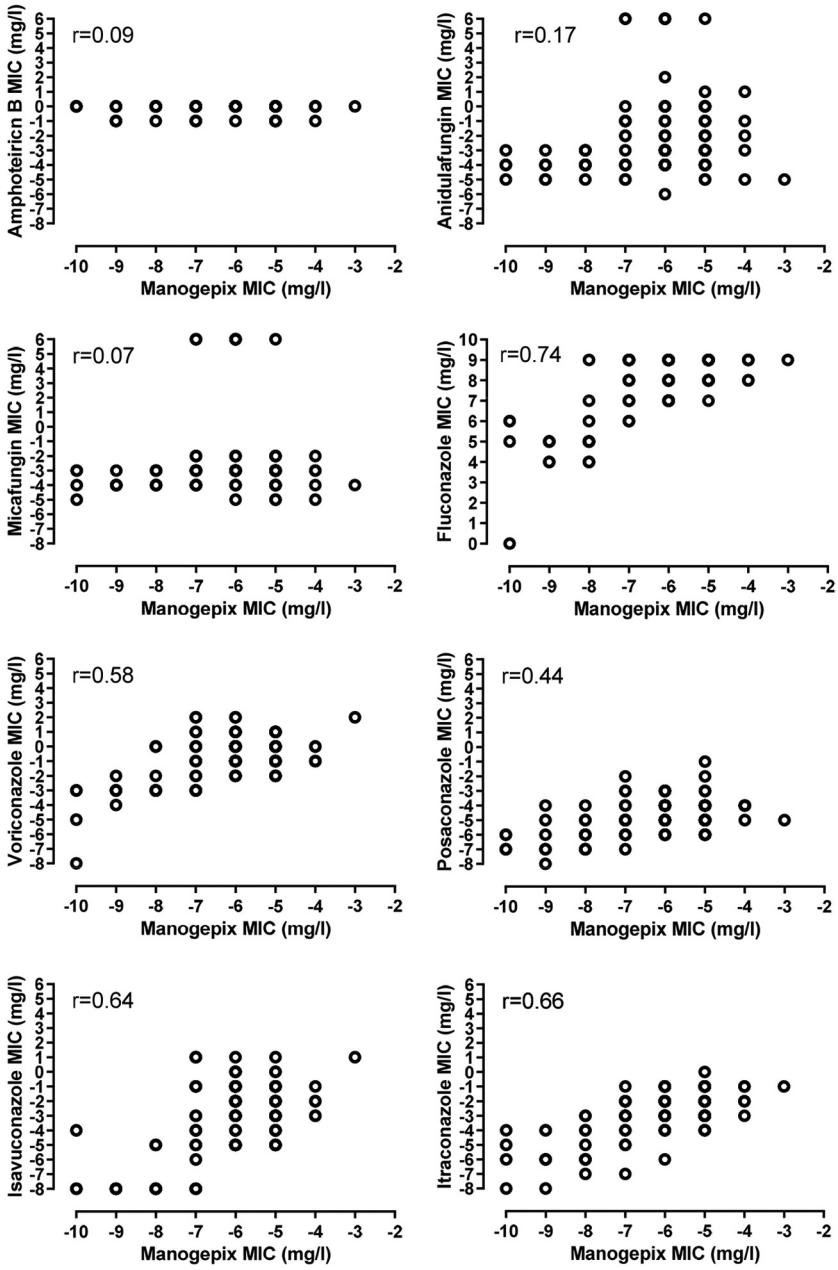


FIG 3 Correlations between manogepix MICs and MICs of the other drugs with the EUCAST methodology. Correlation coefficients are shown.

In conclusion, our study suggests an excellent correlation between EUCAST and CLSI MIC testing of *C. auris*. This is in line with what has been reported for other *Candida* spp. and for moulds (15, 16). It also suggests that the differential MICs found for manogepix reflect true but minor MIC differences. We hypothesize that the differential MICs may be linked to differences in efflux pump expression associated with concomitant fluconazole resistance and, thus, that what is perceived as the wild-type population is likely a mix of true wild-type and non-wild-type isolates with low-grade resistance mechanisms, which may complicate the establishment of epidemiological cutoff values. Further analysis of patient outcomes versus *C. auris* manogepix MICs is necessary to understand the clinical implications of strains with elevated MICs. Overall, the *in vitro* activity of manogepix was highly potent on a mg/liter basis. This is particularly promising due to the multidrug resistance potential associated with *C. auris*.

MATERIALS AND METHODS

Fungal isolates. A total of 122 clinical isolates of *C. auris* were collected from individual patients in 6 tertiary care hospitals in India from 2010 to 2015 (17). The isolates were mainly from patients with candidemia (blood, $n = 100$), and the remaining isolates ($n = 22$) were from invasive *Candida* infections, with the types of specimens including tissue and pleural fluid and a single isolate from pus.

Species identification. The isolates were subjected to sequencing of the internal transcribed spacer (ITS) region of the ribosomal subunit as described previously, followed by GenBank basic local alignment search tool (BLAST) pairwise sequence alignment (https://www.ncbi.nlm.nih.gov/BLAST/Blast.cgi) (7). Further, upon subculture on CHROMagar for 24 h at 37°C, all isolates were also identified using matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) (Bruker Daltonics, Bremen, Germany). The ethanol-formic acid extraction procedure was followed according to the manufacturer's protocol for the identification of yeast isolates (7, 18). The spectra were analyzed using Flex Control 3.1 software (Bruker Daltonics, Inc., Billerica, MA, USA) and MALDI Biotyper OC version 3.1 (Bruker Daltonics, Bremen, Germany). The isolates were identified as *C. auris* with a score of >2 against the *C. auris* database (in-house and Bruker's) (7, 18).

Susceptibility testing. CLSI susceptibility testing was performed according to the M27-A3/S4 guidelines (19). EUCAST manogepix MICs have previously been reported for these isolates, as have the EUCAST and CLSI MICs for the comparator compounds (2). Manogepix (APX001A; Amplyx Pharmaceuticals, San Diego, USA) was prepared in dimethyl sulfoxide (DMSO) (5,000 mg/liter; Sigma-Aldrich, Brøndby, Denmark). The final drug concentration ranges studied were 0.001 to 0.5 mg/liter. Drug-free and yeast-free controls were included, and microtiter plates were incubated at 35°C and read visually for the CLSI method (19). The recommended *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019 were used as quality control strains. The MIC end points for azoles and echinocandins were defined as the lowest drug concentration that caused a prominent decrease in visual growth (CLSI) or ≤50% growth (EUCAST) in relation to the growth og the controls. For amphotericin B, the MIC was defined as the lowest concentration at which there was full inhibition of visual growth (CLSI) or ≤10% growth (EUCAST) compared with the growth in the drug-free control wells. MICs for the licensed compounds were classified as wild type and non-wild type by adopting the EUCAST ECOFFs valid 4 February 2020 (www.eucast.org).

Comparison between CLSI and EUCAST. MIC ranges, modal MICs (the most common MIC), MIC_{50}s (the MIC value that includes 50% of the isolates), and MIC_{90}s (the MIC value that includes 90% of the isolates) were calculated using GraphPad Prism version 6.00 (GraphPad software). High off-scale EUCAST MIC results were converted to the next-highest 2-fold dilution, and low off-scale MIC results were left unchanged for comparison between the two methods. The median (range) differences and the 90th percentile of absolute differences were calculated. The percentages of absolute (±0 2-fold dilutions) and essential (±1 and ±2 2-fold dilutions) agreement between the EUCAST and the CLSI methods were calculated for each compound. Wild-type upper limits (WT-ULs), defined as the upper MIC where the wild-type distribution ends, were determined for manogepix using a statistical method and 97.5% and 99% endpoints and the EUCAST ECOFFinder program (20). However, as the values reported here are not formally accepted EUCAST manogepix ECOFFs, we used the term "WT-UL" to avoid confusion.

Any statistical differences between CLSI and EUCAST MICs were investigated using repeated-measures analysis of variance (ANOVA) on $\log_2$ MICs followed by Bonferroni's multiple-comparison test (significance was set at $P < 0.05$). Correlations between the CLSI and EUCAST $\log_2$ MICs of each drug and between manogepix MICs and the MICs of the other drugs using the CLSI and EUCAST methodologies were determined with Pearson analysis for each drug after $\log_2$ transformation.

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Outside this work, the authors have the following potential conflicts to declare. M.C.A. has, over the past 5 years, received research grants/contract work (paid to the SSI) from Amplyx, Basilea, Cidara, F2G, Gilead, Novabiotics, Scynexis, and T2Biosystems and speaker honoraria (personal fee) from Astellas, Gilead, Novartis, MSD, and Seges. She is the current chairman of the EUCAST-AFST. A.C. has no conflicts to declare. K.M.J. has received travel grants from Amplyx Pharmaceuticals and F2G and a meeting grant from MSD. J.M. has, over the past 5 years, received research grants/contract work (paid to the NKUA) from F2G, Gilead, Astellas, Gilead, Pfizer, MSD, and VenatoRx. He is the current clinical data coordinator of the EUCAST-AFST.

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